WHAT IS CLAIMED IS:

1. A method of determining the effect of a drug lead on the activity of a drug-metabolizing enzyme comprising:

(a) providing a drug lead that modifies the stability of a receptor regulating cytochrome P450 expression; and

(b) screening the drug lead for its ability to further modify the stability of the receptor in the presence of one or more co-regulators;

wherein a further modification of stability of the receptor in the presence of the drug lead and a co-regulator of said one or more co-regulators indicates whether the drug lead increases the activity of a drug-metabolizing enzyme.

2. The method of claim 1, wherein providing a drug lead that modifies the stability of the receptor comprises screening one or more of a multiplicity of different molecules for their ability to modify the stability of the receptor.

3. The method of claim 2, wherein said screening of one or more of a multiplicity of different molecules comprises:

(a) contacting said receptor regulating cytochrome P450 and one or more molecules in each of a multiplicity of containers;

(b) treating said receptor in each of said multiplicity of containers to cause said receptor to unfold;

(c) measuring in each of said containers a physical change associated with the unfolding of said receptor;

(d) generating an unfolding curve for said receptor for each of said containers;

(e) comparing each of said unfolding curves in step (d) to:

(i) each of the other unfolding curves; and/or

(ii) the unfolding curve for said target molecule in the absence of any of said multiplicity of molecules; and

(f) determining whether any of said multiplicity of molecules modifies the stability of said receptor, wherein a modification in stability is indicated by a change in said unfolding curve.

4. The method of claim 1 or claim 3, wherein said screening step further comprises:

(a) contacting said drug lead and said receptor regulating cytochrome P450 expression with one or more of said co-regulators in each of a multiplicity of containers;

(b) treating said receptor in each of said multiplicity of containers to cause said receptor to unfold;

(c) measuring in each of said containers a physical change associated with the unfolding of said receptor;

(d) generating an unfolding curve for said receptor for each of said containers;

(e) comparing each of said unfolding curves in step (d) to:

(i) each of the other unfolding curves; and/or

(ii) the unfolding curve for said receptor in the absence of (1) said drug lead and/or (2) said co-regulators; and

(f) determining whether said drug lead further modifies the stability of said receptor, wherein a further modification in stability is indicated by a further change in said unfolding curve.

5. The method of claim 1 wherein the one or more co-regulators includes a co-activator and/or co-repressor.

6. The method according to claim 1, wherein the molecule further modifies the stability of the receptor in the presence of a co-activator, thereby identifying the ligand as an agonist of the receptor when in the presence of the co-activator.

7. The method according to claim 6, wherein the agonist is a partial agonist.

8. The method according to claim 1, wherein the molecule further modifies the stability of the receptor in the presence of a co-repressor, thereby identifying the ligand as a non-agonist of the receptor when in the presence of the co-activator.

9. The method according to claim 8, wherein the non-agonist is a partial agonist.

10. A method of determining the effect of a drug lead on the activity of a drug-metabolizing enzyme comprising:

(a) providing a drug lead that shifts the thermal unfolding curve of a receptor regulating cytochrome P450 expression; and

(b) screening the drug lead for its ability to further shift the thermal unfolding curve of the receptor in the presence of one or more co-regulators;

wherein a further shift in the thermal unfolding curve of the receptor in the presence of the drug lead and a co-regulator of said one or more co-regulators indicates whether the drug lead increases the activity of a drug-metabolizing enzyme.

11. The method of claim 10, wherein providing a drug lead that shifts the thermal unfolding curve of the receptor comprises screening one or more of a multiplicity of different molecules for their ability to shift the thermal unfolding curve of the receptor.

12. The method of claim 11, wherein said screening of one or more of a multiplicity of different molecules comprises:

(a) contacting said receptor regulating cytochrome P450 and one or more molecules in each of a multiplicity of containers;

(b) heating said receptor in each of said multiplicity of containers to cause said receptor to unfold;

(c) measuring in each of said containers a physical change associated with the thermal unfolding of said receptor;

(d) generating a thermal unfolding curve for said receptor for each of said containers;

(e) comparing each of said thermal unfolding curves in step (d) to:

(i) each of the other thermal unfolding curves; and/or

(ii) the thermal unfolding curve for said target molecule in the absence of any of said multiplicity of molecules; and

(f) determining whether any of said multiplicity of molecules shifts the thermal unfolding curve of said receptor.

13. The method of claim 10 or claim 12, wherein said screening step further comprises:

(a) contacting said drug lead and said receptor regulating cytochrome P450 expression with one or more of said co-regulators in each of a multiplicity of containers;

(b) heating said receptor in each of said multiplicity of containers to cause said receptor to unfold;

(c) measuring in each of said containers a physical change associated with the thermal unfolding of said receptor;

(d) generating a thermal unfolding curve for said receptor for each of said containers;

(e) comparing each of said thermal unfolding curves in step (d) to:

(i) each of the other thermal unfolding curves; and/or

(ii) the thermal unfolding curve for said receptor in the absence of (1) said drug lead and/or (2) said co-regulators; and

(f) determining whether said drug lead further shifts the thermal unfolding curve of said receptor.

14. The method of claim 10 wherein the one or more co-regulators includes a co-activator and/or co-repressor.

15. The method according to claim 10, wherein the molecule further modifies the stability of the receptor in the presence of a co-activator, thereby identifying the ligand as an agonist of the receptor when in the presence of the co-activator.

16. The method according to claim 15, wherein the agonist is a partial agonist.

17. The method according to claim 10, wherein the molecule further modifies the stability of the receptor in the presence of a co-repressor, thereby identifying the ligand as a non-agonist of the receptor when in the presence of the co-activator.

18. The method according to claim 17, wherein the non-agonist is a partial agonist.

19. A method of identifying an agonist of xenobiotic metabolism comprising screening a molecule for its ability to modify the stability of a receptor regulating cytochrome P450 expression and to further modify the stability of said receptor when in the presence of one or more co-activators; wherein a molecule that modifies the stability of said receptor and further modifies the stability of said receptor when in the presence of a co-activator is identified as an agonist of xenobiotic metabolism.

20. The method of claim 19, wherein said screening step further comprises:

(a) contacting said molecule and said receptor regulating cytochrome P450 expression with one or more of said co-activators in each of a multiplicity of containers;

(b) treating said receptor in each of said multiplicity of containers to cause said receptor to unfold;

(c) measuring in each of said containers a physical change associated with the

unfolding of said receptor;

(d) generating an unfolding curve for said receptor for each of said containers;

(e) comparing each of said unfolding curves in step (d) to:

(i) each of the other unfolding curves; and/or

(ii) the unfolding curve for said receptor in the absence of (1) said molecule and/or (2) said co-activators; and

(f) determining whether said molecule further modifies the stability of said receptor, wherein a further modification in stability is indicated by a further change in said unfolding curve.

21. A method according to claim 19, wherein the agonist is a partial agonist.

22. A method of identifying an agonist of xenobiotic metabolism comprising screening a molecule for its ability to shift the thermal unfolding curve of a receptor regulating cytochrome P450 expression and to further shift the thermal unfolding curve of said receptor when in the presence of one or more co-activators; wherein a molecule that shifts the thermal unfolding curve of said receptor and further shifts the thermal unfolding curve of said receptor when in the presence of a co-activator is identified as an agonist of xenobiotic metabolism.

23. The method of claim 22, wherein said screening step further comprises:

(a) contacting said molecule and said receptor regulating cytochrome P450 expression with one or more of said co-activators in each of a multiplicity of containers;

(b) heating said receptor in each of said multiplicity of containers to cause said receptor to unfold;

(c) measuring in each of said containers a physical change associated with the thermal unfolding of said receptor;

(d) generating a thermal unfolding curve for said receptor for each of said containers;

(e) comparing each of said thermal unfolding curves in step (d) to:

(i) each of the other thermal unfolding curves; and/or

(ii) the thermal unfolding curve for said receptor in the absence of (1) said molecule and/or (2) said co-activators; and

(f) determining whether said molecule further modifies the stability of said receptor, wherein a further modification in stability is indicated by a further change in said unfolding curve.

24. A method according to claim 22, wherein the agonist is a partial agonist.

25. A method of identifying a non-agonist of xenobiotic metabolism comprising screening a molecule for its ability to modify the stability of a receptor regulating cytochrome P450 expression; wherein a molecule that does not modify the stability of said receptor is identified as a non-agonist of xenobiotic metabolism.

26. The method of claim 25, wherein said screening step comprises:

(a) contacting said receptor regulating cytochrome P450 and one or more molecules in each of a multiplicity of containers;

(b) treating said receptor in each of said multiplicity of containers to cause said receptor to unfold;

(c) measuring in each of said containers a physical change associated with the unfolding of said receptor;

(d) generating an unfolding curve for said receptor for each of said containers;

(e) comparing each of said unfolding curves in step (d) to:

(i) each of the other unfolding curves; and/or

(ii) the unfolding curve for said target molecule in the absence of any of said multiplicity of molecules; and

(f) determining whether said molecule modifies the stability of said receptor, wherein a modification in stability is indicated by a further change in said unfolding curve.

27. A method of identifying a non-agonist of xenobiotic metabolism comprising screening a molecule for its ability to shift the thermal unfolding curve of a receptor regulating cytochrome P450 expression; wherein a molecule that does not shift the thermal unfolding curve of said receptor is identified as a non-agonist of xenobiotic metabolism.

28. The method of claim 27, wherein said screening step comprises:

(a) contacting said receptor regulating cytochrome P450 and one or more molecules in each of a multiplicity of containers;

(b) heating said receptor in each of said multiplicity of containers to cause said receptor to unfold;

(c) measuring in each of said containers a physical change associated with the thermal unfolding of said receptor;

(d) generating a thermal unfolding curve for said receptor for each of said containers;

(e) comparing each of said thermal unfolding curves in step (d) to:

(i) each of the other thermal unfolding curves; and/or

(ii) the thermal unfolding curve for said target molecule in the absence of any of said multiplicity of molecules; and

(f) determining whether said molecule modifies the thermal unfolding curve of said receptor.

29. A method of identifying non-agonists of xenobiotic metabolism comprising:

(a) screening one or more of a multiplicity of molecules for their ability to modify the stability of a receptor regulating cytochrome P450 expression; wherein molecules that do not modify the stability of said receptor are identified as non-agonists of xenobiotic metabolism; and

(b) screening molecules from step (a) that modify the stability of said receptor for their ability to further modify the stability of said receptor when in the presence of one or more co-repressors; wherein molecules that further modify the stability of said receptor when in the presence of a co-repressor are identified as non-agonists of xenobiotic metabolism.

30. A method of identifying non-agonists of xenobiotic metabolism comprising:

(a) screening one or more of a multiplicity of molecules for their ability to shift the thermal unfolding curve of a receptor regulating cytochrome P450 expression; wherein molecules that do not shift the thermal unfolding curve of said receptor are identified as non-agonists of xenobiotic metabolism; and

(b) screening molecules from step (a) that shift the thermal unfolding curve of said receptor for their ability to further shift the thermal unfolding curve of said receptor when in the presence of one or more co-repressors; wherein molecules that further shift the thermal unfolding curve of said receptor when in the presence of a co-

repressor are identified as non-agonists of xenobiotic metabolism.

31. The method of claim 30, wherein said screening step (b) further comprises:

(a) contacting said molecule and said receptor regulating cytochrome P450 expression with one or more of said co-activators in each of a multiplicity of containers;

(b) treating said receptor in each of said multiplicity of containers to cause said receptor to unfold;

(c) measuring in each of said containers a physical change associated with the unfolding of said receptor;

(d) generating an unfolding curve for said receptor for each of said containers;

(e) comparing each of said unfolding curves in step (d) to:

(i) each of the other unfolding curves; and/or

(ii) the unfolding curve for said receptor in the absence of (1) said molecule and/or (2) said co-activators; and

(f) determining whether said molecule further modifies the stability of said receptor, wherein a further modification in stability is indicated by a further change in said unfolding curve.

32. A method according to claim 30, wherein the non-agonist is a partial agonist.

33. A method of identifying an agonist of drug clearance comprising: screening a molecule for its ability to modify the stability of a receptor regulating expression of a drug transport protein and to further modify the stability of said receptor when in the presence of one or more co-activators; wherein a molecule that modifies the stability of said receptor and further modifies the stability of said receptor when in the presence of a co-activator is identified as an agonist of drug clearance.

34. The method of claim 33, wherein said screening step further comprises:

(a) contacting said molecule and said receptor regulating cytochrome P450 expression with one or more of said co-activators in each of a multiplicity of containers;

(b) treating said receptor in each of said multiplicity of containers to cause said receptor to unfold;

(c) measuring in each of said containers a physical change associated with the

unfolding of said receptor;

(d) generating an unfolding curve for said receptor for each of said containers;

(e) comparing each of said unfolding curves in step (d) to:

(i) each of the other unfolding curves; and/or

(ii) the unfolding curve for said receptor in the absence of (1) said molecule and/or (2) said co-activators; and

(f) determining whether said molecule further modifies the stability of said receptor, wherein a further modification in stability is indicated by a further change in said unfolding curve.

35. A method according to claim 33, wherein the agonist is a partial agonist.

36. A method of identifying an agonist of drug clearance comprising: screening a molecule for its ability to shift the thermal unfolding curve of a receptor regulating expression of a drug transport protein and to further shift the thermal unfolding curve of said receptor when in the presence of one or more co-activators; wherein a molecule that shifts the thermal unfolding curve of said receptor and further shifts the thermal unfolding curve of said receptor when in the presence of a co-activator is identified as an agonist of drug clearance.

37. The method of claim 36, wherein said screening step (b) further comprises:

(a) contacting said molecule and said receptor regulating cytochrome P450 expression with one or more of said co-activators in each of a multiplicity of containers;

(b) heating said receptor in each of said multiplicity of containers to cause said receptor to unfold;

(c) measuring in each of said containers a physical change associated with the thermal unfolding of said receptor;

(d) generating a thermal unfolding curve for said receptor for each of said containers;

(e) comparing each of said thermal unfolding curves in step (d) to:

(i) each of the other thermal unfolding curves; and/or

(ii) the thermal unfolding curve for said receptor in the absence of (1) said molecule and/or (2) said co-activators; and

(f) determining whether said molecule shifts the thermal unfolding curve of said receptor.

38. A method according to claim 36, wherein the agonist is a partial agonist.

39. A method of determining the effect of a drug lead on the activity of drug efflux comprising: providing a drug lead that modifies the stability of a receptor regulating expression of a drug transport protein and screening the drug lead for its ability to further modify the stability of the receptor in the presence of one or more co-regulators; wherein a further modification of stability of the receptor in the presence of the drug lead and a co-regulator of said one or more co-regulators indicates whether the drug lead increases the activity of drug efflux.

40. The method of claim 39, wherein providing a drug lead that modifies the stability of the receptor comprises screening one or more of a multiplicity of different molecules for their ability to modify the stability of the receptor.

41. The method of claim 40, wherein said screening of one or more of a multiplicity of different molecules comprises:

(a) contacting said receptor regulating cytochrome P450 and one or more molecules in each of a multiplicity of containers;

(b) treating said receptor in each of said multiplicity of containers to cause said receptor to unfold;

(c) measuring in each of said containers a physical change associated with the unfolding of said receptor;

(d) generating an unfolding curve for said receptor for each of said containers;

(e) comparing each of said unfolding curves in step (d) to:

(i) each of the other unfolding curves; and/or

(ii) the unfolding curve for said target molecule in the absence of any of said multiplicity of molecules; and

(f) determining whether any of said multiplicity of molecules modifies the stability of said receptor, wherein a modification in stability is indicated by a change in said unfolding curve.

42. The method of claim 39 or claim 40, wherein said screening step further comprises:

(a) contacting said drug lead and said receptor regulating cytochrome P450 expression with one or more of said co-regulators in each of a multiplicity of containers;

(b) treating said receptor in each of said multiplicity of containers to cause said receptor to unfold;

(c) measuring in each of said containers a physical change associated with the unfolding of said receptor;

(d) generating an unfolding curve for said receptor for each of said containers;

(e) comparing each of said unfolding curves in step (d) to:

(i) each of the other unfolding curves; and/or

(ii) the unfolding curve for said receptor in the absence of (1) said drug lead and/or (2) said co-regulators; and

(f) determining whether said drug lead further modifies the stability of said receptor, wherein a further modification in stability is indicated by a further change in said unfolding curve.

43. The method of claim 39 wherein the one or more co-regulators includes a co-activator and/or co-repressor.

44. The method according to claim 39, wherein the molecule further modifies the stability of the receptor in the presence of a co-activator, thereby identifying the ligand as an agonist of the receptor when in the presence of the co-activator.

45. The method according to claim 44, wherein the agonist is a partial agonist.

46. The method according to claim 39, wherein the molecule further modifies the stability of the receptor in the presence of a co-repressor, thereby identifying the ligand as a non-agonist of the receptor when in the presence of the co-activator.

47. The method according to claim 46, wherein the non-agonist is a partial agonist.

48. A method of determining the effect of a drug lead on the activity of drug efflux comprising:

(a) providing a drug lead that shifts the thermal unfolding curve of a receptor regulating expression of a drug transport protein; and

(b) screening the drug lead for its ability to further shift the thermal unfolding curve of the receptor in the presence of one or more co-regulators;

wherein a further shift in the thermal unfolding curve of the receptor in the presence of the drug lead and a co-regulator of said one or more co-regulators indicates whether the drug lead increases the activity of drug-efflux.

49. The method of claim 48, wherein providing a drug lead that shifts the thermal unfolding curve of the receptor comprises screening one or more of a multiplicity of different molecules for their ability to shift the thermal unfolding curve of the receptor.

50. The method of claim 49, wherein said screening of one or more of a multiplicity of different molecules comprises:

(a) contacting said receptor regulating cytochrome P450 and one or more molecules in each of a multiplicity of containers;

(b) heating said receptor in each of said multiplicity of containers to cause said receptor to unfold;

(c) measuring in each of said containers a physical change associated with the thermal unfolding of said receptor;

(d) generating a thermal unfolding curve for said receptor for each of said containers;

(e) comparing each of said thermal unfolding curves in step (d) to:

(i) each of the other thermal unfolding curves; and/or

(ii) the thermal unfolding curve for said target molecule in the absence of any of said multiplicity of molecules; and

(f) determining whether any of said multiplicity of molecules shifts the thermal unfolding curve.

51. The method of claim 48 or claim 50, wherein said screening step further comprises:

(a) contacting said drug lead and said receptor regulating cytochrome P450 expression with one or more of said co-regulators in each of a multiplicity of containers;

(b) heating said receptor in each of said multiplicity of containers to cause said receptor to unfold;

(c) measuring in each of said containers a physical change associated with the thermal unfolding of said receptor;

(d) generating a thermal unfolding curve for said receptor for each of said containers;

(e) comparing each of said thermal unfolding curves in step (d) to:

(i) each of the other thermal unfolding curves; and/or

(ii) the thermal unfolding curve for said receptor in the absence of (1) said drug lead and/or (2) said co-regulators; and

(f) determining whether said drug lead further modifies the stability of said receptor, wherein a further modification in stability is indicated by a further change in said unfolding curve.

52. The method of claim 48 wherein the one or more co-regulators includes a co-activator and/or co-repressor.

53. The method according to claim 48, wherein the molecule further modifies the stability of the receptor in the presence of a co-activator, thereby identifying the ligand as an agonist of the receptor when in the presence of the co-activator.

54. The method according to claim 53, wherein the agonist is a partial agonist.

55. The method according to claim 48, wherein the molecule further modifies the stability of the receptor in the presence of a co-repressor, thereby identifying the ligand as a non-agonist of the receptor when in the presence of the co-activator.

56. The method according to claim 55, wherein the non-agonist is a partial agonist.

57. The method of any one of claims 1-56, wherein the receptor is SXR or PXR.

58. The method of any one of claims 1-56, wherein the receptor is Ah, XRE, CAR, or PPAR-α.

59. A method of determining the effect of a molecule on xenobiotic metabolism and/or drug clearance comprising: screening a molecule for its ability to modify the stability of the SXR receptor and to further modify the stability of said receptor when in the presence of one or more co-regulators; wherein a further modification of stability of the receptor in the presence of the molecule and a co-regulator of said one or more co-regulators indicates whether the molecule is an agonist or an antagonist of xenobiotic metabolism and/or drug clearance.

60. A method of determining the effect of a molecule on xenobiotic metabolism and/or drug clearance comprising: screening a molecule for its ability to shift the

thermal unfolding curve of the SXR receptor and to further shift the thermal unfolding curve of said receptor when in the presence of one or more co-regulators; wherein a further shift of the thermal unfolding curve of the receptor in the presence of the molecule and a co-regulator of said one or more co-regulators indicates whether the molecule is an agonist or an antagonist of xenobiotic metabolism and/or drug clearance.

61. A method according to any of claims 1-60, wherein the co-regulator is a co-activator and/or a co-repressor.

62. A method according to any of claims 1-60, wherein an agonist for a co-regulator dependent receptor is a strong inducer.

63. A method according to claim 62, wherein the strong inducer is 11-α-hydroxyprogesterone.

64. A method according to claim 62, wherein the strong inducer has a binding affinity of less than about 5 μM and a statistical probability of agonist state of about 0.8 to about 1.0.

65. A method according to any of claims 1-60, wherein a partial agonist of a co-regulator dependent receptor is a weak inducer.

66. A method according to claim 65, wherein the weak inducer has a binding affinity of less than about 5 μM and a statistical probability of agonist state of about 0.4 to about 0.8.

67. a method according to claim 65, wherein the weak inducer has a binding affinity of at least about 5 μM and a statistical probability of agonist state of about 0.4 to about 1.0.

68. A method according to any of claims 1-60, wherein an antagonist of a co-regulator dependent receptor is a non-inducer.

69. A method according to claim 68, wherein the non-inducer has a binding affinity of less than about 5 μM and a statistical probability of agonist state of less than about 0.4.

70. a method according to claim 65, wherein the non-inducer has a binding affinity of at least about 5 μM and a statistical probability of agonist state of less than about 0.4.